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ORIGINAL RESEARCH

Effect of Heart Rate on 1-Year Outcome for Patients With Acute Ischemic Stroke

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BACKGROUND: Previous literature about the effect of heart rate on poststroke outcomes is limited. We attempted to elucidate (1) whether heart rate during the acute period of ischemic stroke predicts subsequent major clinical events, (2) which heart rate parameter is best for prediction, and (3) what is the estimated heart rate cutoff point for the primary outcome.

METHODS AND RESULTS: Eight thousand thirty-one patients with acute ischemic stroke who were hospitalized within 48 hours of onset were analyzed retrospectively. Heart rates between the 4th and 7th day after onset were collected and heart rate parameters including mean, time-weighted average, maximum, and minimum heart rate were evaluated. The primary outcome was the composite of recurrent stroke, myocardial infarction, and mortality up to 1 year after stroke onset. All heart rate parameters were associated with the primary outcome (*P*'s<0.001). Maximum heart rate had the highest predictive power. The estimated cutoff point for the primary outcome was 81 beats per minute for mean heart rate and 100 beats per minute for maximum heart rate. Patients with heart rates above these cutoff points had a higher risk of the primary outcome (adjusted hazard ratio, 1.80 [95% CI, 1.57–2.06] for maximum heart rate and 1.65 [95% CI, 1.45–1.89] for mean heart rate). The associations were replicated in a separate validation dataset (N=10 000).

CONCLUSIONS: These findings suggest that heart rate during the acute period of ischemic stroke is a predictor of major clinical events, and optimal heart rate control might be a target for preventing subsequent cardiovascular events.

Key Words: acute ischemic stroke ■ cohort study ■ heart rate ■ prognosis

In contradistinction to blood pressure, where there are specific guidelines for management of this metric after acute ischemic stroke (AIS),[1] guidance for the management of heart rate after AIS is not well established. The largest study on this topic was a post-hoc analysis of the PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial, which included >20 000 ischemic stroke cases and reported that a higher heart rate was associated with increased mortality.[2] However, this post-hoc analysis had limitations. First, the PROFESS trial enrolled patients who had experienced stroke within 90 days of

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CLINICAL PERSPECTIVE

What Is New?

- In this retrospective analysis of 8031 acute ischemic stroke cases, heart rate between the fourth and seventh day after stroke onset was nonlinearly associated with the composite of recurrent stroke, myocardial infarction, and death.
- Maximum heart rate had the best predictive power for adverse events.
- Maximum heart rate of 100 beats per minute and mean rate of 81 beats per minute were determined as cutoffs.

What Are the Clinical Implications?

- Heart rate during the acute period of ischemic stroke was associated with future adverse cardiovascular events.
- A specific cutoff could be implemented in clinical practice or clinical trials.

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
bpm	beats per minute
CRCS-K	Clinical Research Collaboration for Stroke in Korea registry
PROFESS	Prevention Regimen for Effectively Avoiding Second Strokes trial
SBP	systolic blood pressure

randomization; therefore, this study could not analyze the effect of heart rate obtained during the acute period of stroke. Second, because the PROFESS trial excluded patients with indications for anticoagulants with intention to compare aspirin and dipyridamole versus clopidogrel, the study results might not be applicable to patients with cardioembolic stroke.[3]

In a recent analysis that we carried out for patients with AIS and atrial fibrillation (AF), heart rate during the acute period was associated with poststroke mortality.[4] Considering this result together with the post-hoc analysis of the PROFESS trial, it may be reasonable to generalize the effect of heart rate on poststroke outcomes to all AIS populations, although there is no direct evidence.

Our study aimed to elucidate whether heart rate obtained during the acute period of stroke is associated with subsequent major clinical events up to 1-year poststroke and the nature of the association. Furthermore, we also aimed to determine which heart rate parameter best predicts outcomes and its optimal target for clinical practice and future trials.

METHODS

Data Availability

The anonymized data from this study may be shared after approval from the local institutional review board with qualified researchers carrying out legitimate research by contacting the lead investigator (H-JB at braindoc@snu.ac.kr).

Study Population

Patients with AIS admitted to 14 hospitals participating in the CRCS-K (Clinical Research Collaboration for Stroke in Korea) registry between January 2011 and November 2014 were eligible for the study. Among them, the following participants were included for the study. Those who: (1) were admitted within 48 hours of symptom onset, (2) had a relevant ischemic brain lesion on magnetic resonance imaging or computed tomography of the head, and (3) had heart rate data between the 4th and 7th day from onset of stroke. Those whose heart rate was collected <5 times and had no outcome data were excluded. Baseline characteristics, including demographics, risk factors, and acute treatment including reperfusion therapy and discharge medication, were collected during hospitalization. Stroke severity at admission was measured using the National Institutes of Health Stroke Scale, and stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment classification with some modification.[5] A separate dataset consisting of 10 000 patients with AIS who were hospitalized and registered in the CRCS-K registry between September 2015 and October 2018 and met the identical eligibility criteria was established for validation.

Collection of Heart Rate Data

Heart rate data collected through routine clinical practice during hospitalization because of index stroke were extracted retrospectively from the electronic medical record systems of the participating centers. Heart rate data between the 4th and 7th day after stroke onset were analyzed. Heart rate during the first 3 days after stroke was not analyzed because it might reflect the effect of a stress reaction to stroke.[4] For those who were discharged within 7 days of stroke onset, heart rate data until discharge were used. Heart rate data were summarized into 4 parameters: arithmetic mean, time-weighted average, and minimum and maximum heart rate. The time-weighted average was calculated by summing the average heart rate between 2 time points by the time interval between 2 time points,

which is the area under the curve in the time–heart rate graph, and dividing it by total elapsed time.[6] Minimum and maximum heart rates were the highest and lowest heart rates among the heart rates that were captured between the 4th and 7th day after stroke onset.

Outcomes and Ascertainment of Outcomes

The primary outcome of the study was the composite of recurrent stroke, myocardial infarction, and all-cause mortality. Secondary outcomes were all-cause mortality, recurrent stroke, and the composite of recurrent stroke, myocardial infarction, and vascular death. Vascular death was defined as any death during the index stroke admission, death caused by recurrent stroke, myocardial infarction or congestive heart failure, or sudden death without an identifiable nonvascular cause.[7] Outcome events were ascertained prospectively for 1 year after the index stroke by surveillance of medical records or structured telephone interviews conducted by trained stroke coordinators at each participating center. Because heart rate data were collected during the first 7 days after stroke, outcome ascertainment was started at the 8th day of stroke. The detailed protocols were described elsewhere.[8,9] The collection of clinical information for the CRCS-K registry was approved by the local institutional review boards in all participating centers with a waiver for patient consent because of the use of anonymized data and minimal risk to participants. We obtained additional approval for this study. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[10]

Statistical Analysis

Missing values were treated with multiple imputations by creating 10 multiple imputed datasets, and the pooled estimate was presented as a result. Each heart rate parameter was categorized as deciles and the cumulative incidence of outcomes was estimated using the Kaplan–Meier product-limit method and compared among the deciles using the log-rank test. Since a nonlinear association was previously suggested between heart rate and outcomes,[2,4] a multivariable Cox proportional hazards model with restricted cubic spines of 4 knots was constructed with each heart rate parameter and predetermined covariates. Predetermined covariates included age, sex, time from symptom onset to hospital arrival, initial stroke severity measured as National Institutes of Health Stroke Scale score, history of hypertension, diabetes, dyslipidemia, coronary artery disease, heart failure, previous history of stroke or transient ischemic attack, premorbid modified Rankin scale, current smoking status, whether the patient received recanalization therapy including intravenous thrombolysis or endovascular treatment, antithrombotic administration (antiplatelet agents and/or anticoagulants), statin administration at discharge, symptomatic steno-occlusion of the intra- or extracranial major cerebral arteries, initial systolic blood pressure (SBP), mean value of SBP between the 4th and 7th days after stroke onset, initial glucose level, and ischemic stroke subtype.

Nonlinearity of the associations between the heart rate parameters and outcomes was assessed using the cubic term of the heart rate parameters, while the overall association was assessed using both the linear and cubic terms. The predictive power of each heart rate parameter for the primary outcome and all-cause mortality was assessed using Akaike information criterion, Bayes Information Criterion, and Harrell's C-statistics. An optimal target (ie, cutoff point) for each heart rate parameter was determined using the Contal and O'Quigley method, which was developed to determine cutoff points in survival data by choosing the point that maximizes the log-rank statistics.[11] Hazards below and above the cutoff were derived from a multivariable Cox-frailty model with adjustment for clustering within hospitals. The robustness of the study results was tested by subgroup analysis according to SBP tertiles collected between the 4th and 7th day after stroke onset, age (>70 and ≤70 years), and presence and absence of AF or hypertension. Furthermore, a landmark analysis within or >30 days after starting outcome ascertainment using the time-dependent Cox model was performed. The validation analysis using a separate dataset (2015–2018) was performed.

All statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc, Cary, NC, USA) and R software version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided *P* value <0.05 was considered statistically significant.

RESULTS

Among 18 093 patients with AIS registered between 2011 and 2014, 8031 met the eligibility criteria (Figure S1). The mean age was 68 years, ≈60% of the patients were men, 1 fourth had AF, half had steno-occlusion of the major cerebral artery corresponding to the acute ischemic lesions, and the median National Institutes of Health Stroke Scale score at admission was 4 (Table 1). The median (interquartile range) number of heart rate measurements was 18 (12–35), and the mean and SD of the 4 heart rate parameters were 74.0±13.01 beats per minute (bpm) for the arithmetic mean, 73.9±13.01 for the time-weighted average, 91.9±20.9 for maximum heart rate, and 60.3±10.5, for minimum heart rate (Figure S2).

Table 1. Patients' Baseline Characteristics: Comparison Between Main Dataset and Validation Dataset

Variables	Main dataset (N=8031)	Validation dataset (N=10 000)
Age, y	68.1±13.0	68.4±12.9
Male sex	4703 (58.6)	5946 (59.5)
Hypertension	5631 (70.1)	6310 (63.1)
Diabetes	2603 (32.4)	3043 (30.4)
Dyslipidemia	2482 (30.9)	2544 (25.4)
Atrial fibrillation	1966 (24.5)	2250 (22.5)
Previous stroke or TIA	1791 (22.3)	2077 (20.8)
Current smoking	2050 (25.5)	2291 (22.9)
Coronary heart disease	720 (9.0)	922 (9.2)
Heart failure	171 (2.1)	178 (1.8)
Premorbid mRS		
0	6006 (74.8)	8242 (82.4)
1	589 (7.3)	616 (6.2)
2	463 (5.8)	464 (4.6)
3	491 (6.1)	395 (3.9)
4	264 (3.3)	211 (2.1)
5	218 (2.7)	73 (0.7)
Onset to arrival time	5 (2–17)	5 (2–17)
Initial NIHSS score	4 (2–11)	4 (2–9)
Hyperacute treatment		
Intravenous thrombolysis	1378 (17.2)	1642 (16.4)
Endovascular thrombectomy	788 (9.8)	1101 (11.0)
Stroke subtype		
Large artery atherosclerosis	2765 (34.4)	3369 (33.7)
Small vessel occlusion	1367 (17.0)	1724 (17.2)
Cardioembolism	2101 (26.2)	2364 (23.6)
Other-determined	218 (2.7)	368 (3.7)
Undetermined	1580 (19.7)	2175 (21.8)
Symptomatic steno-occlusion of relevant artery	4094 (51.0)	4701 (47.0)
Discharge antiplatelet	6111 (76.1)	7435 (74.4)
Discharge anticoagulant	1798 (22.4)	1974 (19.7)
Discharge statin	6711 (83.6)	8708 (87.1)
Initial SBP, mm Hg	149.4±27.8	148.4±27.7
Mean SBP during 3rd to 7th day after onset, mm Hg	134.0±14.7	135.9±15.6
Initial glucose, mg/dL	142.7±61.2	145.8±60.6

Values are number of patients (%), mean±SD, or median (interquartile range) unless otherwise indicated. mRS indicates modified Rankin's scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; and TIA, transient ischemic attack.

The median follow-up duration was 370 days (interquartile range, 356–392). The 1-year cumulative incidence of outcome events was 13.8% for the primary outcome, 10.9% for all-cause mortality, 3.7% for recurrent stroke, and 5.3% for the vascular composite, the composite of recurrent stroke, myocardial infarction, and vascular death. When the arithmetic mean of heart rate was divided into deciles, the cumulative incidence of the primary outcome, all-cause mortality, and the vascular composite tended to increase with increasing deciles, respectively, and the results were most distinct in the highest 2 deciles. There were no significant differences, however, among deciles for recurrent stroke (Figure 1 and Table S1).

The overall associations between all 4 heart rate parameters and the primary outcome were statistically significant (Figure 2A). Regarding nonlinearity, the relationships between maximum and minimum heart rate and the primary outcome were significant (*P*'s for nonlinear terms=0.008 for maximum heart rate and <0.001 for minimum heart rate), and the relationship appeared more "J-shaped" for minimum heart rate than for maximum heart rate. The nadir was ≈55 bpm for minimum heart rate. The nonlinear relationship was more evident for all-cause mortality in that all 4 heart rate parameters had a significant nonlinear effect on all-cause mortality, and the relationships appeared more "J-shaped" (Figure 2B). However, none of the 4 parameters were associated with recurrent stroke (Figure 2C), and the relationships with the vascular composite were similar to those with the primary outcome (Figure 2D).

We compared heart rate parameters regarding the predictive power of the constructed models. The primary outcome and all-cause mortality were selected as outcomes for prediction based on the analysis results above showing the prominent relationships between heart rate parameters and these 2 outcomes. The model including maximum heart rate had the highest Harrell's C-index for the primary outcome and all-cause mortality, and compared with this model, the models with no heart rate parameters or minimum heart rate were significantly inferior, although the models with arithmetic mean and time-weighted average were comparable (Table 2). The model including time-weighted average heart rate had the lowest Akaike information criterion and Bayes Information Criterion for the primary outcome and the model including maximum heart rate had the lowest Akaike information criterion and Bayes Information Criterion for all-cause mortality.

Regarding the primary outcome, the Contal and O'Quigley method yielded a cutoff point of 81 bpm for mean heart rate and time-weighted average, 100 bpm for maximum heart rate, and 65 bpm for minimum heart rate (Table 3). The adjusted hazard ratio (HR) of each parameter above the obtained cutoff point was highest for maximum heart rate followed by time-weighted average, mean, and minimum heart rate. Similar patterns were observed for all-cause mortality.

The subgroup analysis according to mean SBP tertiles and history of hypertension showed that both SBP and history of hypertension did not affect the

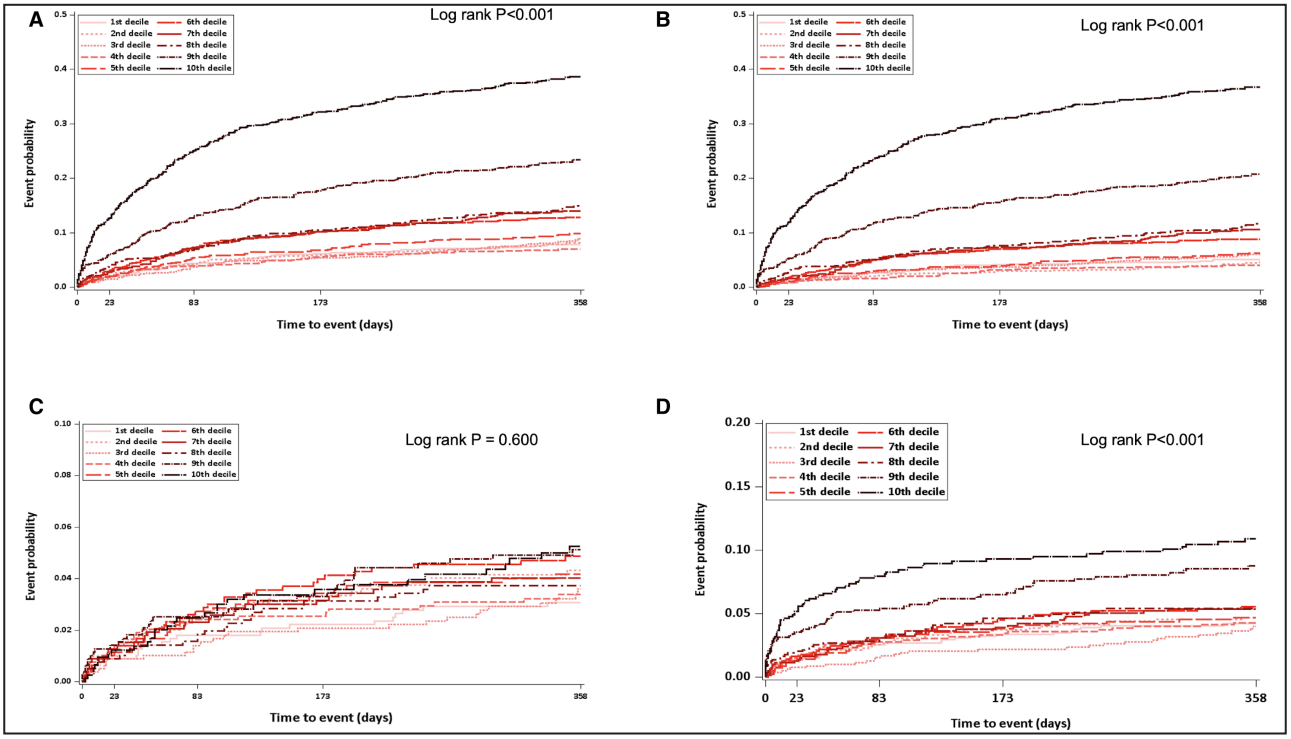

Figure 1. Survival curve of primary and secondary outcomes by mean heart rate deciles.
A, Composite of stroke recurrence, myocardial infarction, and all-cause mortality. **B,** All-cause mortality. **C,** Stroke recurrence. **D,** Composite of stroke recurrence, myocardial infarction, and vascular death.

associations between heart rate parameters and outcomes (Figure S3 through S4). However, patients with AF had a higher risk of the primary outcome at the lower end of each heart rate parameter and a lower risk at the higher end (Figure S5). A similar pattern of effect modification was observed in the subgroup analysis by age for all-cause mortality (Figure S6). In the landmark analysis, risk of the primary outcome consistently increased regardless of heart rate parameters before and after the landmark (Table S2 and Figure S7).

In the validation dataset, the frequency of most vascular risk factors was numerically lower than in the main dataset (Table 1). The 1-year cumulative incidence of the primary outcome or all-cause mortality in the validation dataset was lower than that in the main dataset (10.1% versus 13.8% for the primary outcome and 7.6% versus 10.9% for all-cause mortality). Most results were reproduced with the validation dataset (Table 3 and Figure S8), but the overall strength of the associations between heart rate parameters and outcomes seemed to be attenuated.

DISCUSSION

Our findings indicate that the heart rate parameters obtained between the 4th and 7th day after stroke onset were associated with major clinical events during the first year after AIS. The association was most evident for all-cause mortality, which appears to be the main contributor to the association between heart rate parameters and the primary outcome. Among the heart rate parameters, maximum heart rate was the strongest predictor, while the mean and time-weighted average heart rates were comparable. The cutoff value of 100 bpm for maximum heart rate and 81 bpm for mean and time-weighted average heart rate best predicted outcomes with a >1.5-fold increase in risk, which was reproduced in the validation dataset.

Contrary to plentiful evidence for the effect of heart rate on cardiovascular outcomes in the general population and patients with coronary artery disease,[12–15] only a few studies have evaluated the effect of heart rate on poststroke outcomes. The post-hoc analysis of the PROFESS trial might be the largest study on this topic to date.[2] In this study, higher baseline heart rate was associated with higher risk of mortality but was not associated with stroke recurrence as reproduced here. The adjusted HR of the highest quintile, >82 bpm, was 1.74, which was also similar to the adjusted HR of the mean heart rate >81 bpm in our study (1.88 in the main dataset and 1.70 in the validation dataset). However, the generalizability of the PROFESS post-hoc analysis is limited; it included only patients who had an indication for antiplatelet therapy; therefore, only 3% had AF.

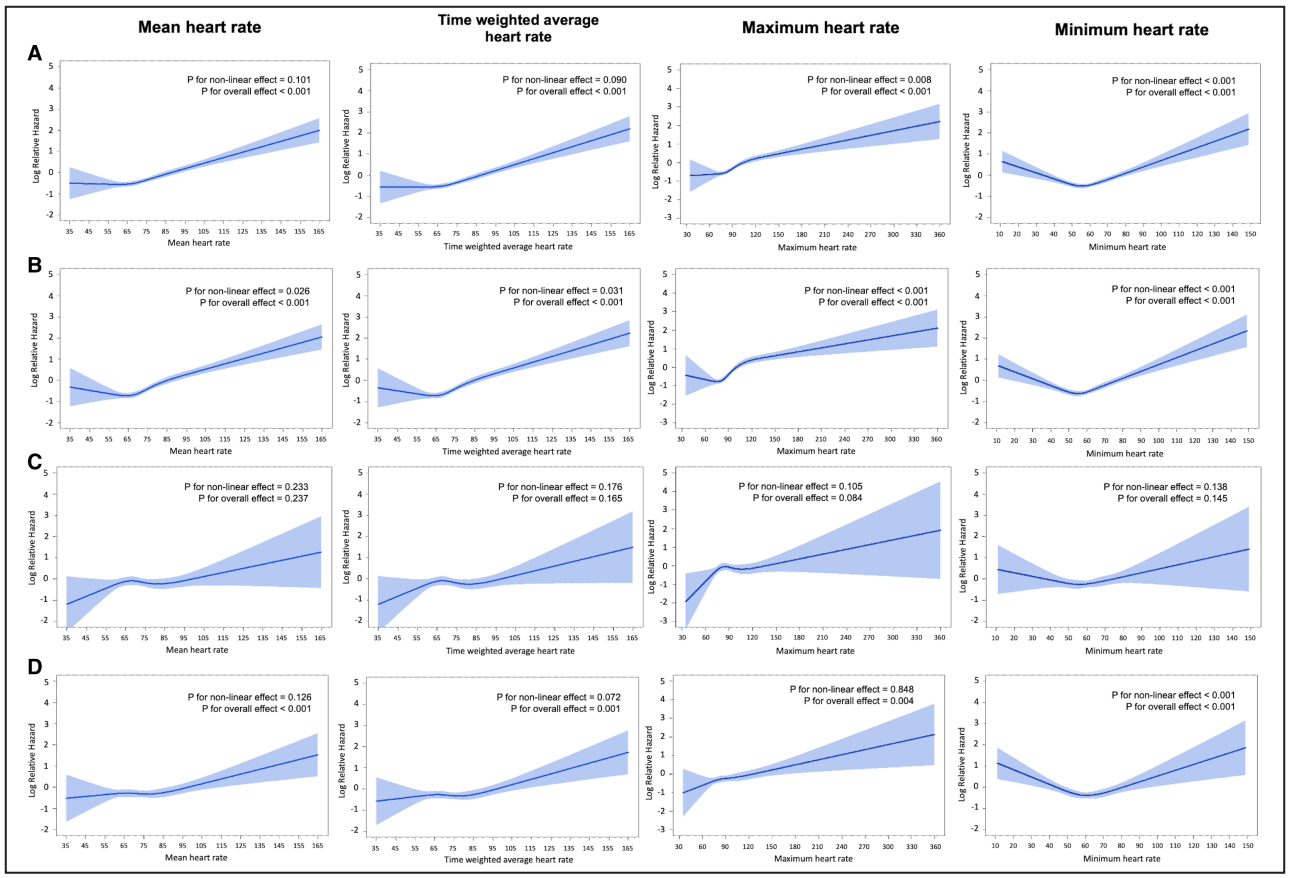

Figure 2. Association between heart rate parameters and outcomes.
A, Composite of stroke recurrence, myocardial infarction, and all-cause mortality. **B,** All-cause mortality. **C,** Stroke recurrence. **D,** Composite of stroke recurrence, myocardial infarction, and vascular death.

Our recent study reported that the mean heart rate had a nonlinear, "J-shaped" relationship with 1-year mortality in patients with AF-related AIS.[4] Furthermore, the patients in the PROFESS trial were enrolled after the acute period of stroke, within 90 days of stroke onset. Our study collected heart rates during days 4 to 7 after

Table 2. Comparison of the Predictive Power for Primary Outcome and All-Cause Mortality Between Heart Rate Parameters

	Composite of stroke recurrence, myocardial infarction, and all-cause mortality				All-cause mortality			
	AIC	BIC	Harrell's C index	*P* value for compared with Model 3 (paired differences in the Harrell's C index)	AIC	BIC	Harrell's C index	*P* value for compared with Model 3 (paired differences in the Harrell's C index)
Model 0	18 571.48	18 706.83	0.7639	<0.001	14 089.51	14 218.35	0.8302	<0.001
Model 1	18 468.39	18 618.78	0.7740	0.213	13 958.29	14 101.45	0.8433	0.062
Model 2	18 460.64	18 611.03	0.7748	0.504	13 950.16	14 093.32	0.8441	0.164
Model 3	18 469.49	18 619.88	0.7758	Ref	13 946.48	14 089.64	0.8464	Ref
Model 4	18 506.46	18 656.86	0.7693	0.002	14 013.48	14 156.64	0.8364	<.001

AIC indicates Akaike information criterion; BIC, Bayes Information Criterion; and SBP, systolic blood pressure.

Model 0: predetermined covariates only; Model 1: Model 0+mean heart rate; Model 2: Model 0+time-weighted average heart rate; Model 3: Model 0+maximum heart rate; Model 4: Model 0+minimum heart rate.

Predetermined covariates included admitted hospital, age, sex, time from symptom onset to hospital arrival, initial stroke severity, history of hypertension, diabetes, dyslipidemia, coronary artery disease, heart failure, previous history of stroke or transient ischemic attack, premorbid modified Rankin's scale, current smoking, whether the patient received recanalization therapy (intravenous thrombolysis or endovascular treatment), antithrombotic (antiplatelet agents and/or anticoagulants) and statin administration at discharge, symptomatic steno-occlusion of the intra- or extracranial major cerebral arteries, initial SBP, mean value of SBP between the 4th and 7th days after symptom onset, initial glucose level, and ischemic stroke subtype.

Table 3. Heart Rate Cutoff and HR of Primary Outcome and All-Cause Mortality

	Heart rate cutoff by Contal and O'Quigley Method (beats per minute)	Main dataset		Validation dataset	
		Adjusted HR* (95% CI)	*P* value	Adjusted HR* (95% CI)	*P* value
Composite of stroke recurrence, myocardial infarction, and all-cause mortality					
Mean heart rate	>81	1.65 (1.45–1.89)	<0.0001	1.50 (1.31–1.73)	<0.0001
Time-weighted average heart rate	>81	1.67 (1.46–1.91)	<0.0001	1.54 (1.34–1.77)	<0.0001
Maximum heart rate	>100	1.80 (1.57–2.06)	<0.0001	1.69 (1.46–1.95)	<0.0001
Minimum heart rate	>65	1.36 (1.20–1.54)	<0.0001	1.23 (1.08–1.40)	0.0020
All-cause mortality					
Mean heart rate	>81	1.88 (1.62–2.17)	<0.0001	1.70 (1.45–1.98)	<0.0001
Time-weighted average heart rate	>80	1.89 (1.63–2.19)	<0.0001	1.65 (1.41–1.93)	<0.0001
Maximum heart rate	>100	2.15 (1.84–2.51)	<0.0001	1.84 (1.57–2.17)	<0.0001
Minimum heart rate	>69	1.68 (1.45–1.95)	<0.0001	1.22 (1.04–1.44)	0.0156

Predetermined covariates included age, sex, time from symptom onset to hospital arrival, initial stroke severity, history of hypertension, diabetes, dyslipidemia, coronary artery disease, heart failure, previous history of stroke or transient ischemia attack, premorbid modified Rankin's scale, current smoking, whether the patient received recanalization therapy (intravenous thrombolysis or endovascular treatment), antithrombotic (antiplatelet agents and/or anticoagulants) and statin administration at discharge, symptomatic steno-occlusion of the intra- or extracranial major cerebral arteries, initial SBP, mean value of SBP between the 4th and 7th days after symptom onset, initial glucose level, and ischemic stroke subtype. HR indicates hazard ratio; and SBP, systolic blood pressure.

*Derived from multivariable Cox-frailty model.

stroke onset and tracked major clinical events for up to 1-year poststroke.

Although we demonstrated an association between heart rate and major clinical events following AIS, a claim of causality cannot be concluded based solely on this association. For example, patients with elevated heart rates may have comorbid conditions, such as infection, dehydration, hyperthyroidism, or arrhythmia that underlie the elevation of the heart rate.[16] Furthermore, higher heart rate may be a marker of elevated sympathetic activity (eg, a stress response to stroke), which leads to pathophysiologic consequences such as endothelial dysfunction, cardiac remodeling, and renin-angiotensin-aldosterone system activation, which may be associated with poor outcomes.[17–19] A high heart rate itself can cause either hypoperfusion or hyperperfusion to ischemic brain regions where cerebral autoregulation is diminished or absent and result in further brain damage and adverse outcomes.[20,21] Otherwise, elevated heart rate was reported to be associated with poststroke disability and cognitive decline.[2,22] Elevated heart rate could induce oxidative stress and endothelial dysfunction, leading to atherosclerosis.[23] Ventricular dysfunction caused by prolonged tachycardia, decreased coronary perfusion, and renal dysfunction also may be a possible explanation for the association between elevated heart rate and adverse outcomes.[23–25] Whether lowering heart rate to a specific target range would be beneficial cannot be answered by our study and requires additional proof from a high-level epidemiological study such as a randomized clinical trial.

The efficacy of β-blockers (antihypertensive agents that lower heart rate) was proven by clinical trials in patients with acute myocardial infarction for prevention of re-infarction and mortality,[26–28] and their use is currently recommended.[14,15] However, for patients with AIS, the efficacy of β-blockers has been deemed inconclusive.[29–32] Our results suggest that it is time to re-open the study of β-blocker administration in patients with AIS with heart rates above our specified cutoff points. Maximum heart rate had the best predictive power among the 4 heart rate parameters. Patients who had ever experienced an episode of heart rate exceeding 100 bpm were at >200% risk of mortality during the first year after stroke.

Interestingly, our findings suggest that even transient tachycardia may be a predictor of future adverse events, a phenomenon that was reported in a study published in 1945.[33] A recent study based on a Chinese cohort also showed that even 1 measurement of high resting heart rate might be associated with higher risk of future mortality.[34] Maximum heart rate of >100 bpm can easily be applied to routine clinical practice and clinical trials.

Nonlinear "J-shaped" relationships between heart rate parameters and the primary outcome or all-cause mortality suggest an increased risk of major clinical events for patients with relatively lower heart rates. Sensitivity analysis according to AF status suggests that the increased risk observed at the lower end of the heart rate continuum may be driven by patients with AF (Figure S5). This phenomenon is consistent with our previous study of patients with AF-related stroke.[4] Decreased cardiac contractility in patients with AF and a low heart rate may be an underlying explanatory mechanism. Moreover, low heart rate itself is known to be a predictor of incident AF.[35]

The attenuated strength of the associations between heart rate and outcomes in the validation dataset could be explained by improvement in poststroke outcomes over time (2011–2014 versus 2015–2018). Also, this improvement might be attributed to lower prevalence of vascular risk factors, better premorbid functional status (Table 1), and improvement in quality of stroke care in South Korea over time.[36,37]

Our study has several limitations. First, this was an observational study and the causal relationship between heart rate and outcomes could not be determined. Second, the participating centers of the CRCS-K registry were mostly tertiary hospitals, limiting the generalizability of the study results. However, the age and sex distribution of the CRCS-K registry was comparable to that of nationwide data of South Korea.[38] Third, heart rate was measured during routine practice, and therefore not by a standardized protocol. Fourth, heart rates and medications after discharge were not considered in our study.

ARTICLE INFORMATION

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Supplemental Material

Appendix S1
Tables S1–S2
Figures S1–S8

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Table S1. Cumulative incidence of outcomes by mean heart rate deciles

	Cumulative incidence (%) (95% CI)			
	Day 23	Day 83	Day 173	Day 358
Composite of stroke recurrence, myocardial infarction and all-cause mortality				
1st decile	1.77 (0.85 - 2.69)	4.34 (2.91 - 5.77)	6.20 (4.50 - 7.90)	7.82 (5.92 - 9.72)
2nd decile	2.13 (1.13 - 3.13)	4.28 (2.87 - 5.69)	5.97 (4.32 - 7.63)	8.15 (6.21 - 10.08)
3rd decile	1.52 (0.66 - 2.37)	3.68 (2.37 - 5.00)	5.39 (3.81 - 6.98)	8.88 (6.84 - 10.91)
4th decile	2.02 (1.04 - 3.00)	3.92 (2.57 - 5.28)	5.49 (3.89 - 7.09)	6.95 (5.16 - 8.74)
5th decile	2.04 (1.05 - 3.02)	5.40 (3.81 - 6.98)	6.75 (4.98 - 8.52)	9.83 (7.70 - 11.97)
6th decile	3.05 (1.85 - 4.25)	7.29 (5.47 - 9.11)	10.18 (8.05 - 12.31)	12.87 (10.50 - 15.24)
7th decile	2.77 (1.63 - 3.91)	7.36 (5.54 - 9.18)	10.13 (8.01 - 12.25)	14.02 (11.56 - 16.48)
8th decile	3.67 (2.36 - 4.98)	7.01 (5.22 - 8.80)	10.52 (8.35 - 12.69)	14.91 (12.35 - 17.47)
9th decile	6.04 (4.39 - 7.70)	13.16 (10.79 - 15.53)	17.65 (14.95 - 20.35)	23.38 (20.35 - 26.41)
10th decile	12.74 (10.42 - 15.07)	25.09 (22.05 - 28.12)	32.20 (28.91 - 35.50)	38.68 (35.21 - 42.14)
All-cause mortality				
1st decile	0.88 (0.23 - 1.53)	2.68 (1.55 - 3.81)	4.14 (2.74 - 5.55)	5.09 (3.53 - 6.64)
2nd decile	1.13 (0.40 - 1.87)	2.02 (1.04 - 2.99)	2.93 (1.75 - 4.11)	4.61 (3.11 - 6.11)
3rd decile	0.88 (0.23 - 1.54)	2.67 (1.54 - 3.80)	3.72 (2.39 - 5.05)	6.05 (4.35 - 7.75)
4th decile	0.76 (0.15 - 1.36)	1.64 (0.76 - 2.53)	3.21 (1.97 - 4.45)	4.01 (2.62 - 5.39)
5th decile	1.02 (0.32 - 1.72)	2.96 (1.77 - 4.15)	3.91 (2.54 - 5.28)	6.30 (4.55 - 8.04)
6th decile	1.78 (0.86 - 2.71)	4.99 (3.47 - 6.52)	6.96 (5.17 - 8.75)	8.83 (6.83 - 10.84)
7th decile	1.64 (0.75 - 2.52)	5.08 (3.55 - 6.62)	7.33 (5.50 - 9.16)	10.56 (8.38 - 12.74)
8th decile	2.66 (1.54 - 3.78)	5.10 (3.56 - 6.64)	7.66 (5.78 - 9.54)	11.64 (9.33 - 13.94)
9th decile	5.29 (3.73 - 6.85)	11.89 (9.62 - 14.16)	15.56 (13.00 - 18.12)	20.76 (17.85 - 23.66)
10th decile	11.98 (9.72 - 14.24)	23.44 (20.47 - 26.40)	30.98 (27.71 - 34.25)	36.76 (33.33 - 40.18)

Stroke recurrence				
1st decile	0.89 (0.23 - 1.55)	1.81 (0.87 - 2.75)	2.22 (1.18 - 3.27)	3.07 (1.83 - 4.30)
2nd decile	1.00 (0.31 - 1.69)	2.41 (1.34 - 3.48)	3.34 (2.08 - 4.61)	4.32 (2.88 - 5.77)
3rd decile	0.89 (0.23 - 1.54)	1.41 (0.58 - 2.24)	2.08 (1.07 - 3.09)	3.60 (2.23 - 4.97)
4th decile	1.39 (0.58 - 2.21)	2.42 (1.34 - 3.49)	2.55 (1.45 - 3.66)	3.38 (2.10 - 4.66)
5th decile	1.15 (0.40 - 1.89)	2.73 (1.58 - 3.89)	3.44 (2.14 - 4.74)	4.17 (2.73 - 5.61)
6th decile	1.28 (0.49 - 2.06)	2.74 (1.58 - 3.89)	3.99 (2.59 - 5.39)	4.88 (3.32 - 6.44)
7th decile	1.14 (0.40 - 1.88)	2.32 (1.26 - 3.38)	3.15 (1.91 - 4.40)	4.02 (2.61 - 5.43)
8th decile	0.90 (0.23 - 1.56)	1.84 (0.88 - 2.79)	3.14 (1.87 - 4.40)	3.73 (2.35 - 5.12)
9th decile	1.41 (0.58 - 2.24)	2.52 (1.40 - 3.64)	3.30 (2.00 - 4.60)	5.14 (3.46 - 6.81)
10th decile	1.23 (0.43 - 2.03)	2.49 (1.32 - 3.66)	3.57 (2.13 - 5.02)	5.26 (3.42 - 7.09)
Composite of stroke recurrence, myocardial infarction and vascular death				
1st decile	1.39 (0.58 - 2.21)	2.56 (1.45 - 3.67)	3.38 (2.10 - 4.65)	4.21 (2.78 - 5.64)
2nd decile	1.26 (0.48 - 2.03)	2.54 (1.44 - 3.63)	3.73 (2.40 - 5.06)	4.71 (3.20 - 6.21)
3rd decile	0.76 (0.15 - 1.37)	1.54 (0.67 - 2.40)	2.21 (1.17 - 3.25)	4.00 (2.56 - 5.44)
4th decile	1.64 (0.76 - 2.53)	2.79 (1.64 - 3.94)	3.32 (2.07 - 4.58)	4.28 (2.85 - 5.72)
5th decile	1.40 (0.58 - 2.22)	3.12 (1.89 - 4.34)	3.82 (2.45 - 5.18)	4.69 (3.17 - 6.21)
6th decile	1.66 (0.77 - 2.56)	3.11 (1.89 - 4.34)	4.50 (3.02 - 5.98)	5.53 (3.88 - 7.18)
7th decile	1.26 (0.48 - 2.04)	3.09 (1.87 - 4.31)	3.93 (2.55 - 5.31)	5.36 (3.74 - 6.97)
8th decile	1.90 (0.95 - 2.85)	3.09 (1.87 - 4.31)	4.66 (3.15 - 6.17)	5.40 (3.77 - 7.03)
9th decile	3.53 (2.25 - 4.82)	5.43 (3.83 - 7.03)	6.50 (4.73 - 8.26)	8.76 (6.67 - 10.84)
10th decile	5.19 (3.62 - 6.76)	7.97 (6.01 - 9.93)	9.34 (7.19 - 11.48)	10.92 (8.55 - 13.30)

Table S2. Piecewise hazard ratios for the primary outcome before and after 30 days since outcome ascertainment

Heart rate parameter	Time from outcome ascertainment			
	0 to 30 days		31 to 358 days	
	Adjusted HR* (95% CI)	P-value	Adjusted HR* (95% CI)	P-value
Mean heart rate (per 10 bpm increase)	1.31 (1.23-1.40)	<.0001	1.24 (1.18-1.31)	<.0001
Time-weighted average heart rate (per 10 bpm increase)	1.33 (1.24-1.42)	<.0001	1.26 (1.19-1.33)	<.0001
Maximum heart rate (per 10 bpm increase)	1.17 (1.13-1.21)	<.0001	1.12 (1.09-1.15)	<.0001
Minimum heart rate (per 10 bpm increase)	1.16 (1.07-1.27)	0.0004	1.13 (1.06-1.21)	0.0002

* Derived from multivariable time dependent Cox model. HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure. Predetermined covariates included age, sex, time from symptom onset to hospital arrival, initial stroke severity, history of hypertension, diabetes, dyslipidemia, coronary artery disease, heart failure, previous history of stroke or transient ischemia attack, premorbid modified Rankin's scale, current smoking, whether the patient received recanalization therapy (intravenous thrombolysis or endovascular treatment), antithrombotic (antiplatelet agents and/or anticoagulants) and statin administration at discharge, symptomatic steno-occlusion of the intra- or extracranial major cerebral arteries, initial SBP, mean value of SBP between the 4^{th} and 7^{th} days after symptom onset, initial glucose level, and ischemic stroke subtype.

Figure S1. Patient selection

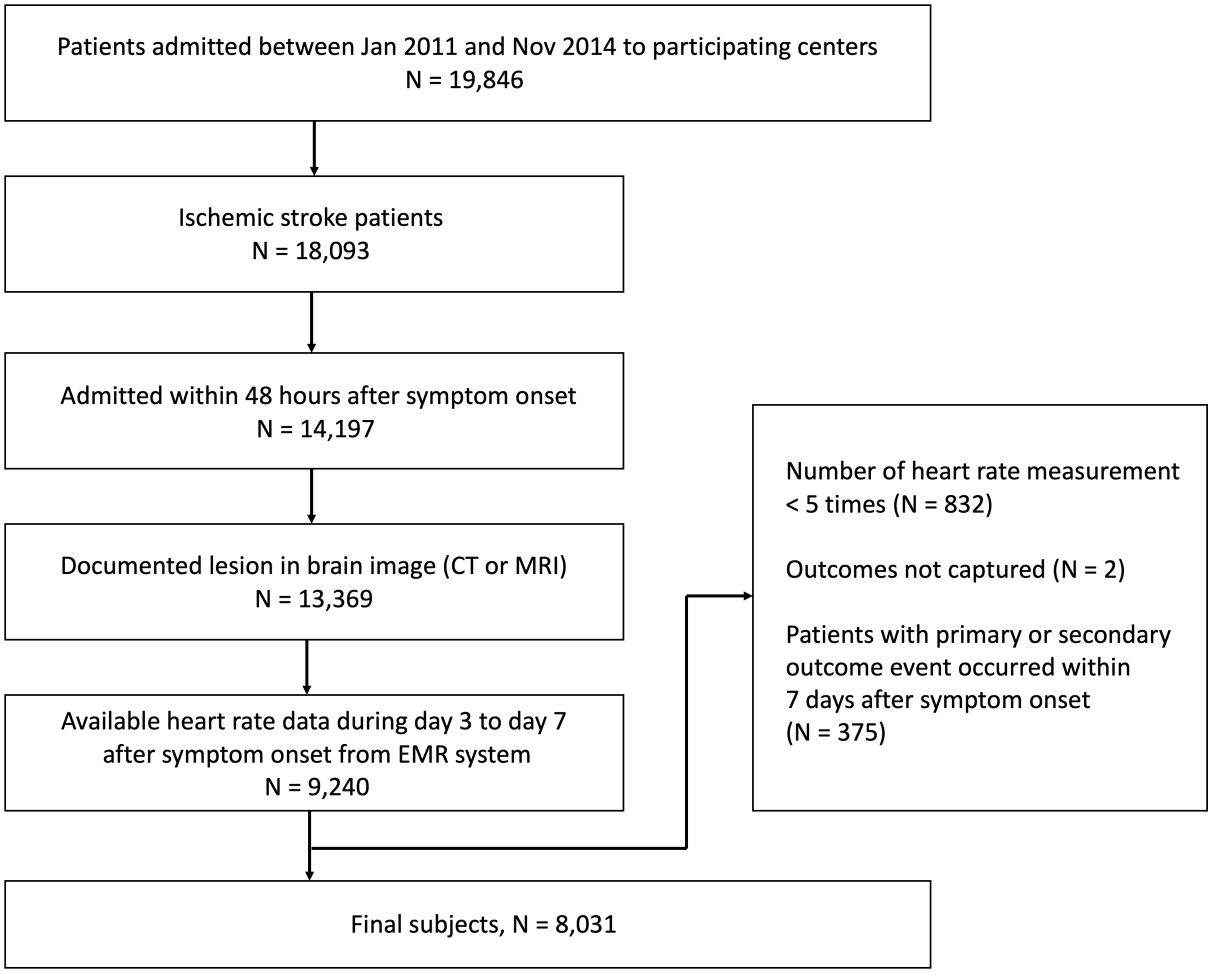

Figure S2. Histogram of heart rate parameters

(A) Mean heart rate (B) time weighted average heart rate (C) Maximum heart rate (D) Minimum heart rate

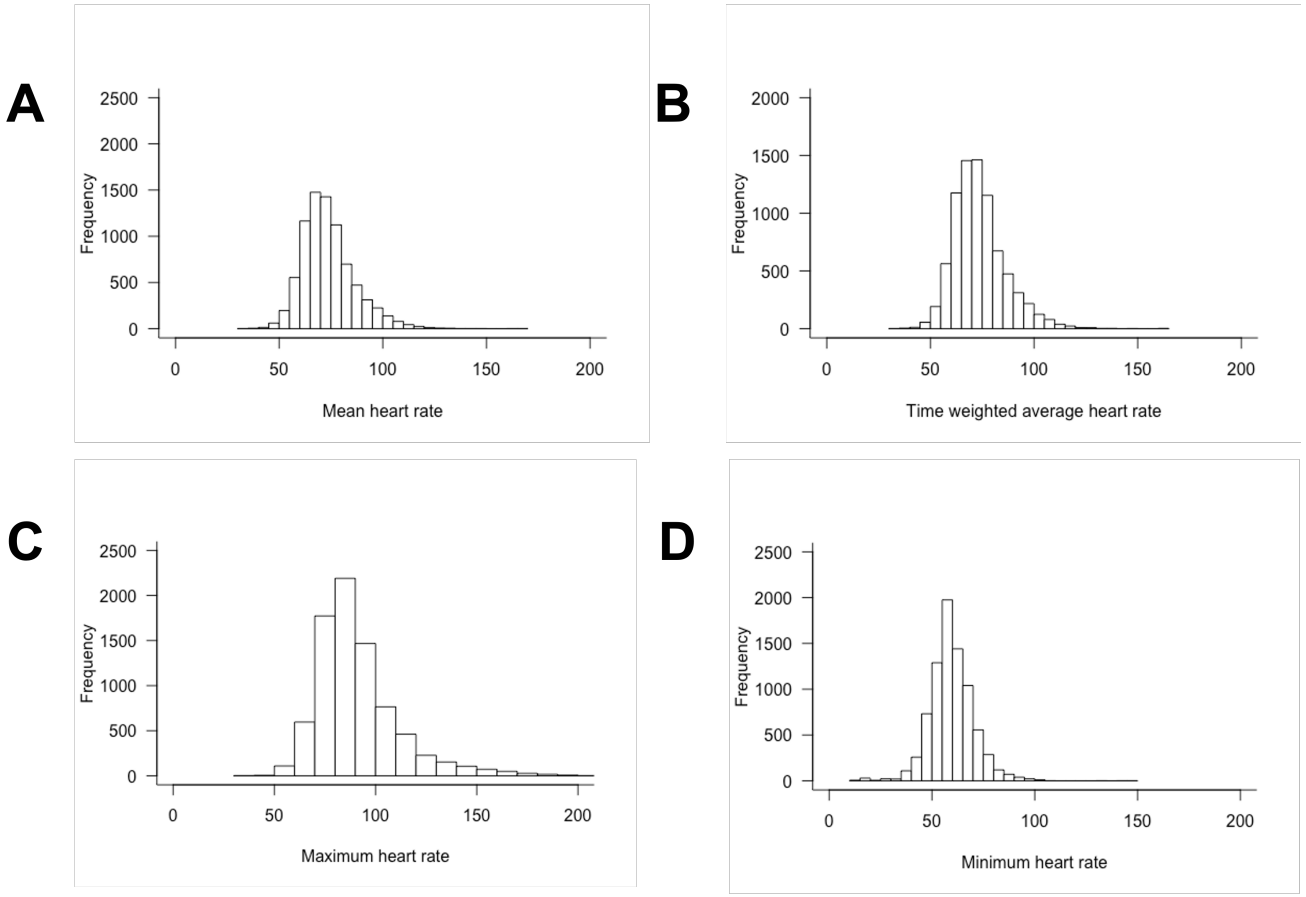

Figure S3. Association between heart rate parameters and primary outcome (A) and all-cause mortality (B) according to mean systolic blood pressure level during day 4 to day 7 after stroke onset

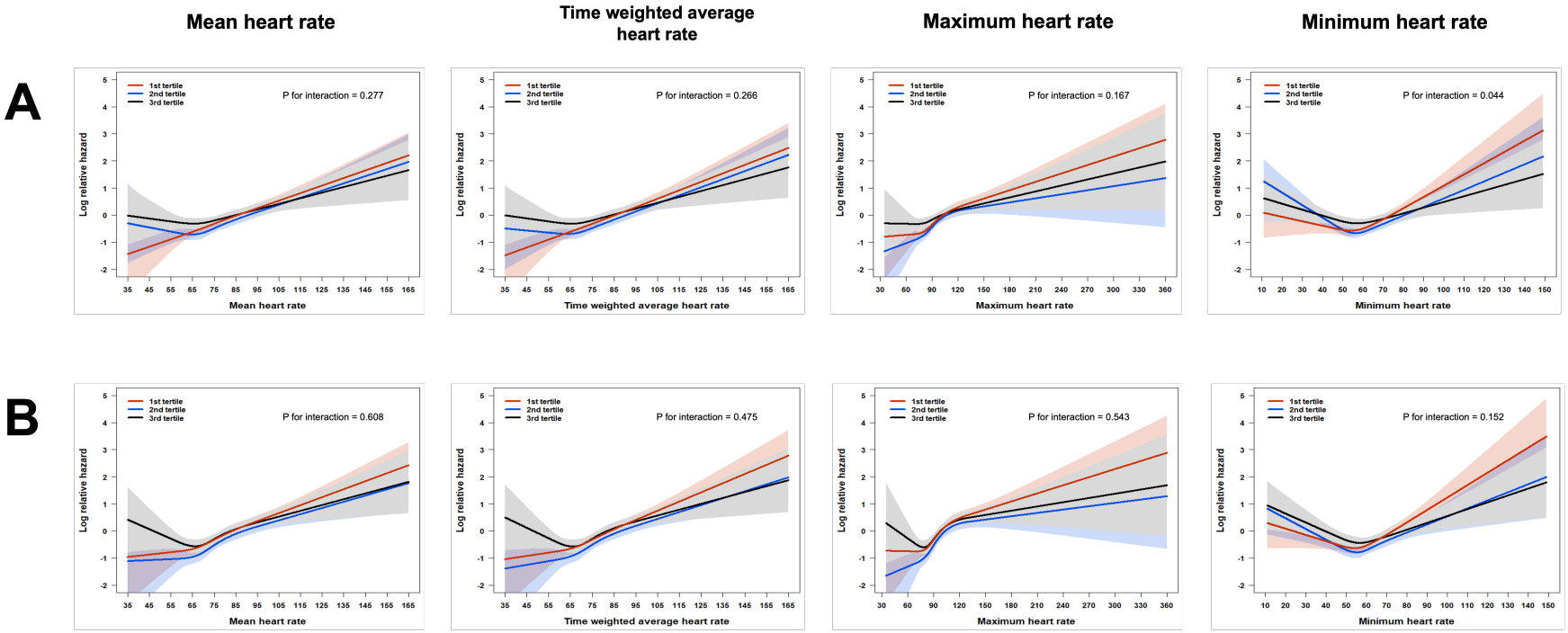

Figure S4. Association between heart rate parameters and primary outcome (A) and all-cause mortality (B) in patients with and without hypertension

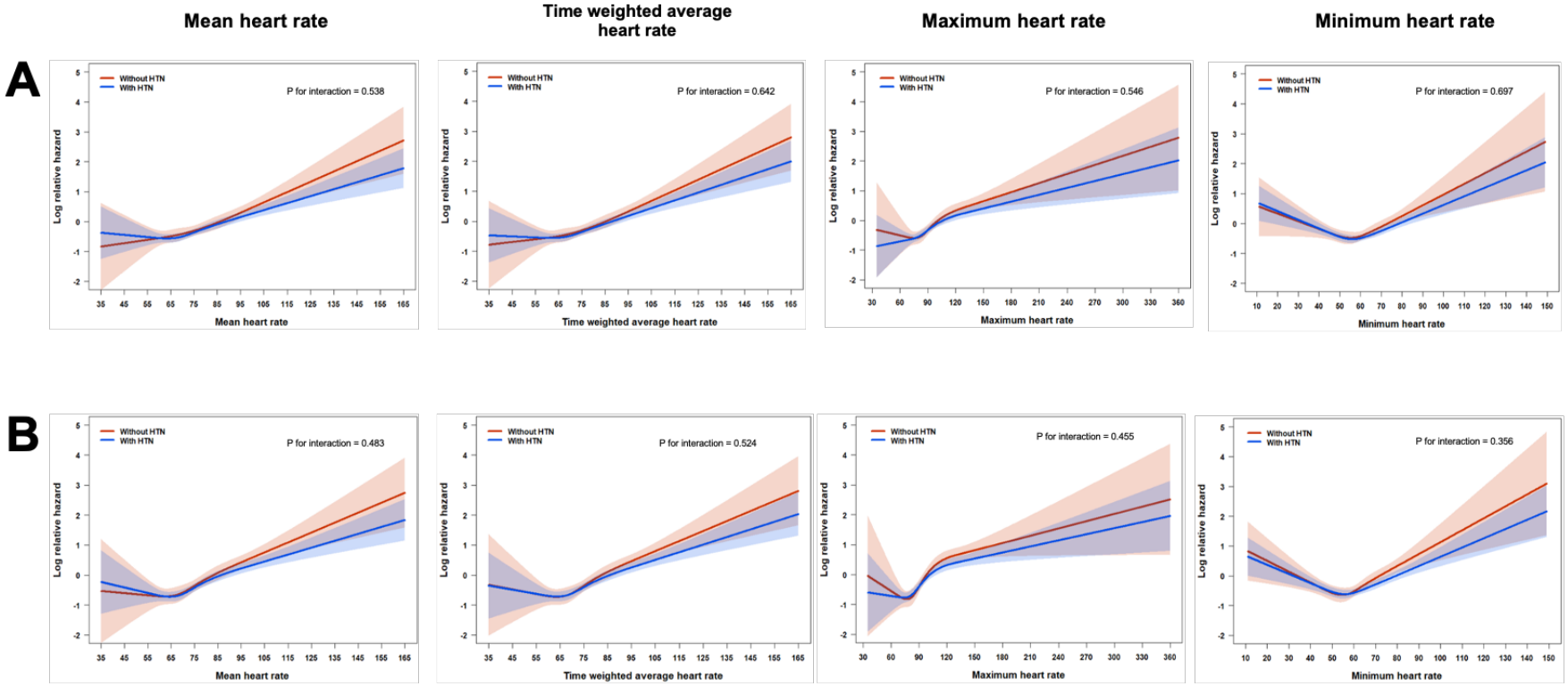

Figure S5. Association between heart rate parameters and primary outcome (A) and all-cause mortality (B) in patients with and without atrial fibrillation

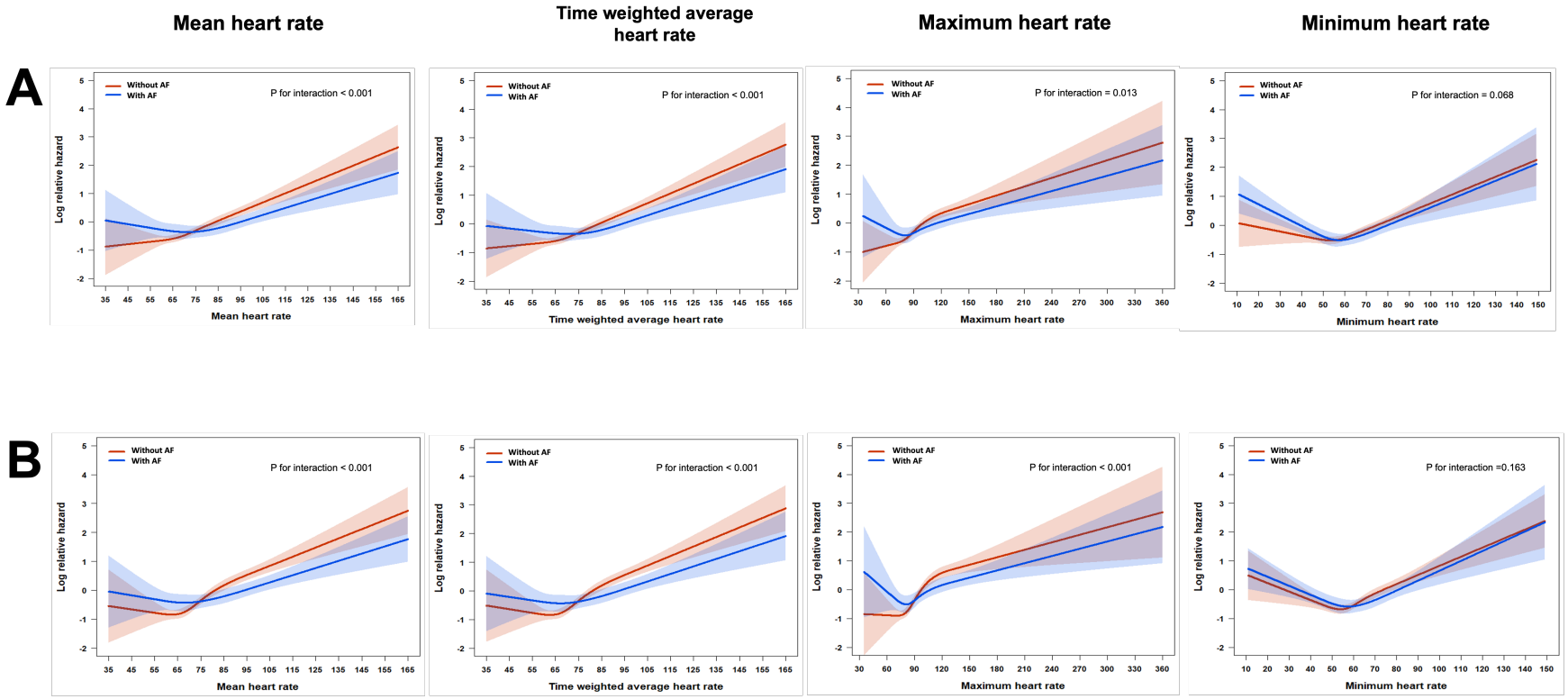

Figure S6. Association between heart rate parameters and primary outcome (A) and all-cause mortality (B) in patients with age older than 70 years and 70 years or younger

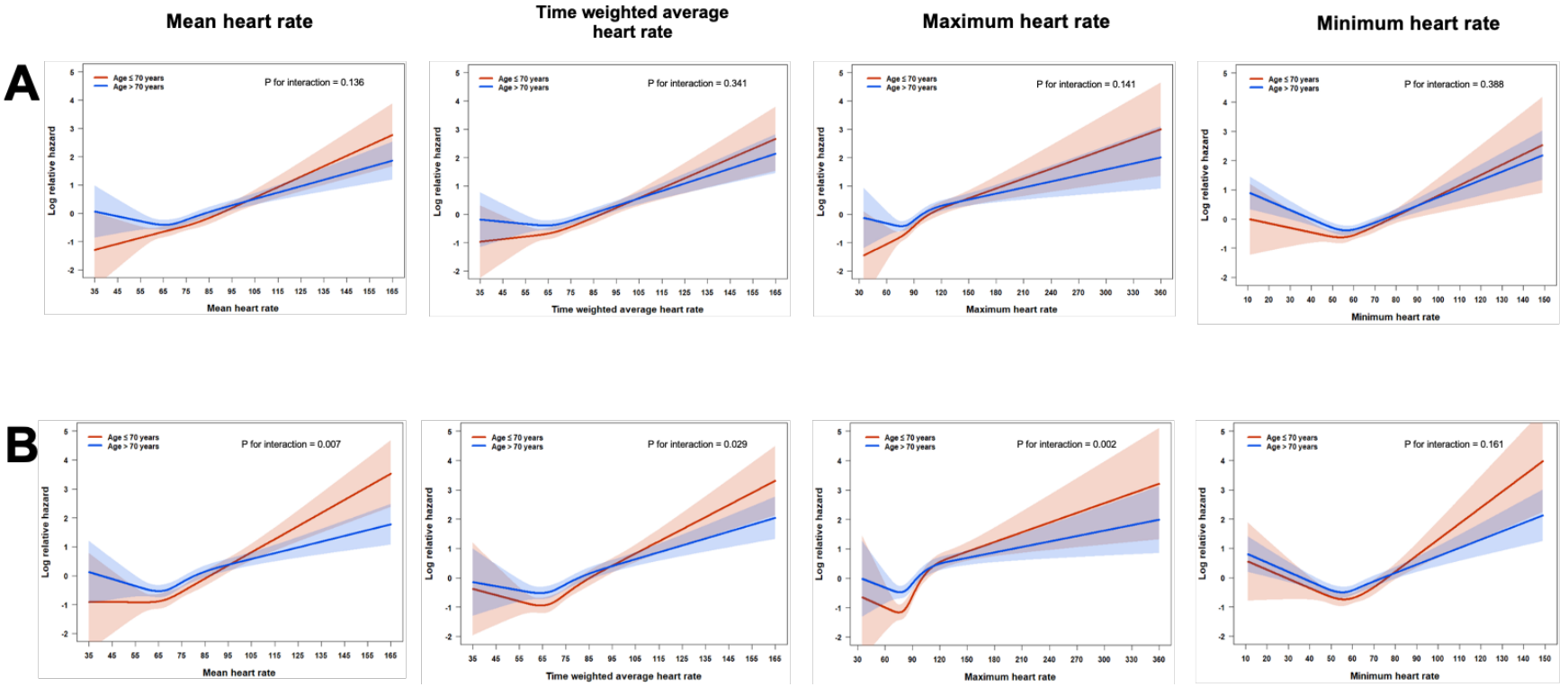

Figure S7. Kaplan-Meier survival curve and piecewise hazard ratios for the primary outcome before and after 30 days since outcome ascertainment according to heart rate cutoffs

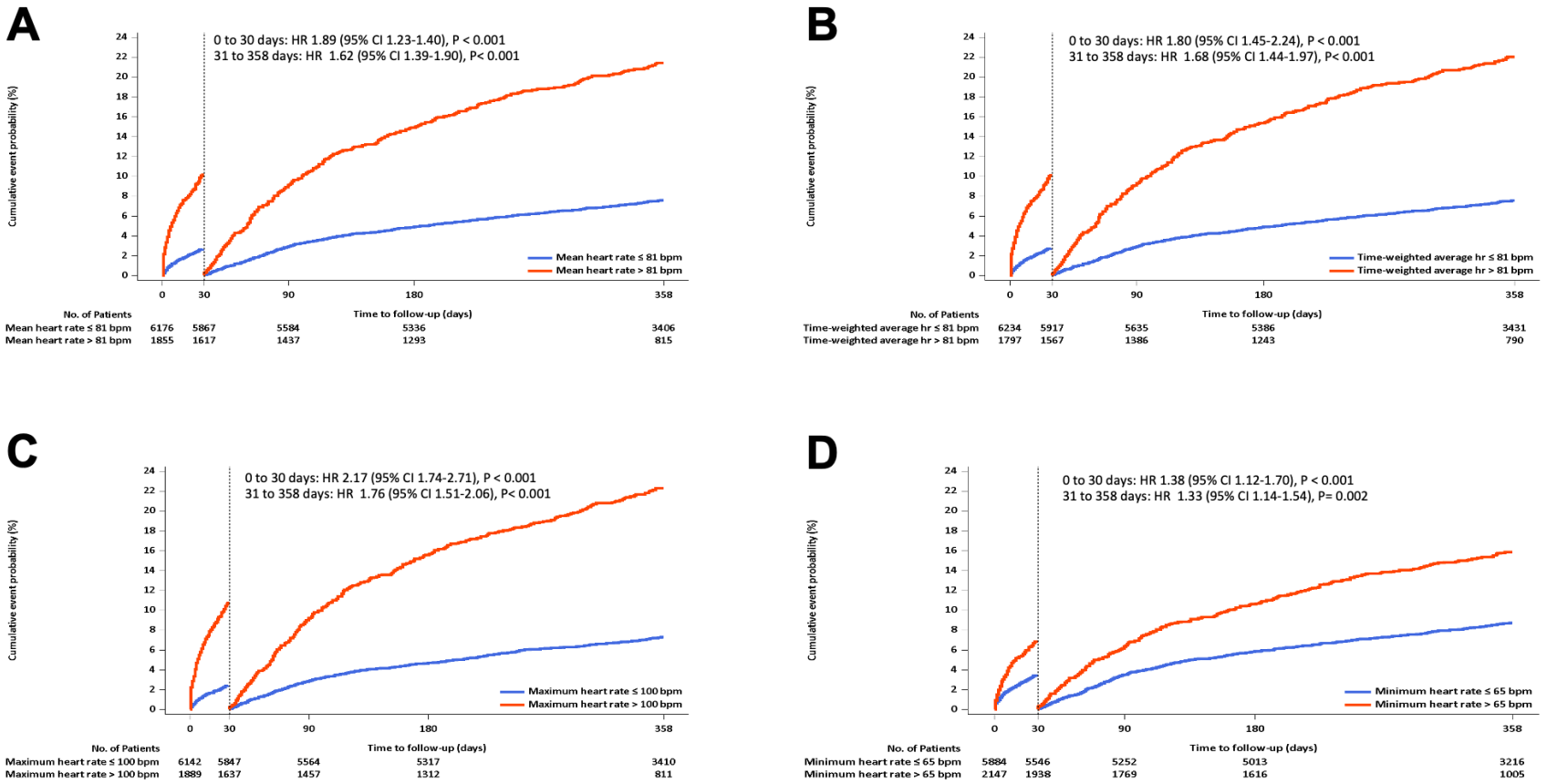

Figure S8. Association between heart rate parameters and primary outcome (A) and all-cause mortality (B) in the validation dataset